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CLINICAL CHARACTERISTICS OF FIRST VENOUS THROMBOSIS AMONG WOMEN UNDER AND OVER 45 YEARS OF AGE

KLINIČKE KARAKTERISTIKE PRVE VENSKE TROMBOZE KOD MLADIH ŽENA I ONIH STARIJIH OD 45 GODINA

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Summary

Introduction. Venous thromboembolism is a multifactorial disease defined by multiple interactions between genetic and acquired risk factors. After coronary heart disease and stroke, venous thromboembolism is the most common cause of cardiovascular death and disability. **Material and Methods**. In order to investigate the clinical characteristics of first venous thromboembolism, 447 women younger than 45 and 174 over 45 years of age with confirmed venous thromboembolism, who had been tested for the presence of thrombophilia in the period 1998-2012, were included in the study. **Results**. Proximal deep vein thrombosis occurred most often among young women, while distal deep vein thrombosis was the most frequent in the older group. The most common reported risk for venous thromboembolism observed in 49.8% of the young women was pregnancy and puerperium, while 25.2% of them developed venous thromboembolism without any obvious cause. Among women over the age of 45, venous thromboembolism developed without an obvious cause in 38.5%, while malignant disease was identified as the most important risk factor in 23% of them. Thrombophilia was observed in 48.7% of the young women in comparison to 28.7% of the older ones ($p < 0.0001$). As for venous thromboembolism recurrence, it developed in 26.3% of young women and 17.8% of the older ones ($p = 0.03$). **Conclusion**. Younger women developed more severe forms of thrombosis than the older ones. Inherited risk factor for thrombosis was detected in almost half of all young women, and in every fourth elderly women. With the exception of factor V Leiden mutation, other types of congenital thrombophilia are almost negligible among older women. Therefore, thrombophilia testing in case of first thrombosis is fully justified only in young women.

Key words: Female; Adult; Aged; Venous Thrombosis; Thromboembolism; Signs and Symptoms; Risk Factors; Diagnostic Techniques and Procedures

Sažetak

Uvod. Venski tromboembolizam je multifaktorijalna bolest koja nastaje u interakciji genetskog i stečenog faktora rizika. Nakon bolesti koronarnih krvnih sudova i moždanog udara, najčešći je razlog kardiovaskularne smrti ili onesposobljenosti. **Materijal i metode.** Sa ciljem da se utvrde kliničke krakteristike prvog venskog tromboembolizma, u studiju je uključeno 447 žena mlađih od 45 i 174 žene starije od 45 godina, koje su testirane na prisustvo trombofilije u periodu 1998−2012. godine. **Rezultati.** Proksimalna duboka venska tromboza češće je zastupljena kod mladih žena, dok je distalna učestalija u grupi starijih. Najčešći faktor rizika za trombozu, koji je utvrđen kod 49,8% mladih žena je trudnoća i stanje posle porođaja, dok se kod 25,2% tromboza razvila bez jasno prepoznatljivog faktora rizika. U grupi starijih žena, tromboza nastaje kod 38,5% bez faktora rizika, dok je malignitet kao najznačajniji faktor rizika utvrđen kod 23%. Prisustvo trombofilije zabeleženo je kod 48,7% mladih, odnosno kod 28,7% starijih žena, $p < 0,001$. Razlika se beleži i u odnosu na ponavljane venske tromboze koje su zabeležene kod 26,3% mladih, odnosno kod 17,8% starijih žena, $p = 0,03$. **Zaključak.** Kod mladih žena se razvijaju klinički teže venske tromboze nego kod starijih. Urođeni faktor rizika otkriven je kod skoro polovine mladih ispitanica, odnosno kod svake četvrte starije žene. Sa izuzetkom faktora V Leiden mutacije ostali tipovi urođene trombofilije su gotovo zanemarljivi u grupi starijih žena. Stoga je testiranje na prisustvo trombofilije u slučaju prve tromboze, u potpunosti opravdano samo kod mlađih žena.

Ključne reči: Žensko; Odrasli; Stari; Venska tromboza; Tromboembolije; Znaci i simptomi; Faktori rizika; Dijagnostičke tehnike i procedure

Introduction

Venous thromboembolism (VTE) is a multifactorial disease and a major cause of morbidity and

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Abbreviations

VTE – venous thromboembolism
CT – computed tomography
AT – antithrombin
PS – protein S
PC – protein C
F – factor
PE – pulmonary embolism
CVT – cerebral vein thrombosis
SVT – superficial vein thrombosis
OC – oral contraceptives
RIETE – Computerized Registry of Patients with Venous Thromboembolism
DVT – deep venous thrombosis

mortality, defined by multiple interactions between genetic (e.g. inherited thrombophilia) and acquired (e.g. age, malignant disease, autoimmune diseases or transient e.g. surgical interventions, fractures, trauma, prolonged immobilization) risk factors [1, 2]. After coronary heart disease and stroke, VTE is the most common cause of cardiovascular death and disability [3]. Transient risk factors for VTE are typical for females and render women more exposed than men to the risk of disease during their lifetime. These include oral contraceptive (OC) use, hormone replacement therapy and pregnancy/puerperium [2]. VTE occurs in one in every 1,000 individuals per year [4], the incidence being lower in individuals under 45 years of age (one of every 10,000) [2]. Survival after VTE is worse than expected, particularly for pulmonary embolism, and another important issue is the development of recurrent VTE [5]. Consequently, VTE has a significant impact on the quality of life since almost half of the patients may develop post-thrombotic syndrome and the cost associated with complications are high [6]. Therefore, the epidemiology of VTE related to the contribution of postulated risk factors and their interaction with VTE in the community has important implications for prevention and management of this serious disease.

Our study was aimed at investigating the clinical characteristics of the first thrombotic event among young women and those over the age of 45 in order to explore possible age dependent differences. Given the difference in the incidence of VTE in individuals up to 45 years of age [2], and the fact that the period of childbearing age in women is the same, statistical analyses were carried out related to the age of 45.

Materials and Methods

The study included 621 consecutive women who were referred from primary health care physicians to two thrombosis centers between January 1998 – June 2013, with the history of VTE to have their anticoagulant treatment followed or to be tested for thrombophilia.

All of them were registered and medical records collected at the first admission were used during the statistical analyses. All women had documented VTE (Doppler ultrasound, lung perfusion scan and helical tomography/computed tomography (CT), and they were tested for thrombophilia presence after anticoagulant therapy cessation. VTE was classified as "provoked" when occurring up to 3 months after the exposure to exogenous risk factors, which included surgery, trauma, immobilization for at least 7 days, OC use, pregnancy-postpartum up to 3 months and malignancy. Women with hepatic, renal or systemic disease were excluded from the study in order to minimize the influence of such diseases or treatment related to them on hemostatic parameters (activity of coagulation factors or natural inhibitors).

As for the age distribution, 447 were younger than 45 when first thrombosis occurred, while 174 were older than 45, their mean age being 29.5 years (ranging from 18 to 45 years) for the former group and 64.5 years (ranging from 45 to 75 years) for the latter one.

The laboratory work-up for thrombophilia included the following tests: biological activity of antithrombin (AT), protein C (PC), protein S (PS), presence of activated protein C resistance (APC-R) and lupus anticoagulants (LA) and factor (F)VIII activity. Deficiencies of natural anticoagulants were defined as less than 75%, 69% and 65% of normal activity for antithrombin, PC, and PS, respectively.

Factor VIII:C was measured by 1-stage clotting assay and levels above 150 IU/dL were considered increased. For the detection of thrombophilia, IL tests (Instrumentation Laboratory, Milan, Italy) were used, and analyses were performed on IL Coagulometers ACL 6000 and Elite Pro. Deoxyribonucleic acid (DNA) analyses for FV Leiden and FII G20210A mutations were conducted by polymerase chain reaction (PCR). The anticardiolipin (aCL) antibodies included determination of anticardiolipin and anti-β2glycoprotein-1 antibodies in both class immunoglobulin G (IgG) and immunoglobulin M (IgM) were determined by ELISA assay using Bindazyme Human Anti IgG and IgM (Binding Site, Birmingham, UK).

The following characteristics regarding the personal or family history, medical records and thrombophilia testing were assessed:

1. Age at time of first VTE
2. Type and localization of VTE - deep venous thrombosis (DVT) - distal or proximal, isolated pulmonary embolism (PE), DVT/PE, thrombosis in an unusual site. Distal thrombosis was considered as thrombosis below the trifurcation [7]
3. The presence of additional risk factors (acquired or transient)
4. The frequency of inherited thrombophilia
5. Time for the first recurrent event

Institutional approval for the study was granted by the Research Ethics Committee of the Blood Transfusion Institute of Serbia (REC number: 5063/3) in accordance with internationally accepted ethical standards and each patient signed the informed consent form.

The analyses were performed using MedCalc, Belgium. Differences between the two groups of women regarding the type/localization, risk factors

for the first VTE and time of the first recurrent event were estimated by the Chi square test, Fisher's test and Student's t-test. The probability value $p<0.05$ was taken into consideration to indicate statistical significance.

Results

The distribution of the type of VTE (distal, proximal, PE or thrombosis in unusual sites) was significantly different in the two groups of women. Thus, proximal DVT ($p<0.0001$) and thrombosis in unusual sites, such as the cerebral vein thrombosis (CVT; $p = 0.03$) were more often present in young women. On the contrary, a somewhat higher rate of distal vein thrombosis was observed in the group of older women, but this was not statistically significant, while the incidence of superficial vein thrombosis (SVT) was significantly higher among the older than among the younger women ($p = 0.04$; **Table 1**).

The rate of spontaneous VTE was found to be higher among the older women than in the group of young women ($p = 0.001$).

As for the acquired risk factors, the most important one affecting 49.8% of the young women was pregnancy/puerperium. Among the older women, malignancy was the most frequent risk for VTE. (**Table 1**). Thrombophilia was observed in 48.7% of the young women compared to 28.7% of the older ones ($p< 0.0001$). Concerning the frequency of congenital thrombophilia, statistically significant differences were recorded between the two groups for inhibitor deficiency ($p = 0.0009$), prothrombin G20210A mutation ($p = 0.04$) or combined thrombophilia ($p = 0.0006$). However, the FV Leiden mutation, as an inherited thrombophilic alteration, was equally represented in both groups of women ($p =0.277$; **Table 2**).

In three-quarters of young carriers of thrombophilia, thrombosis occurred during risk situations, such as pregnancy/puerperium or OC use. On the contrary, in older carriers of thrombophilia, VTE occurrence was equally distributed in groups with and without additional risk factors, ($p= 0.006$; **Graph 1**). Regarding the recurrence of VTE, a statistically significant difference was observed between the two groups, as 26.3% of the young women but only 17.8% of the older women developed recurrent VTE, ($p= 0.03$; **Table 3**).

Discussion

Our results showed that younger women developed proximal deep vein thrombosis or thrombosis in unusual sites such as the cerebral vein more

Table 1. Characteristics of study population
Tabela 1. *Karakteristike ispitanika*

	Young women/*Mlade žene* age/*starost* 18-45	Older women/*Starije žene* age/*starost* 45-75	p
Localization/*lokalizacija* n (%)			
Proximal DVT/*Proksimalna DVT**	120 (26.8)	15 (8.6)	< 0.0001
Distal DVT/*Distalna DVT*	159 (35.5)	75 (43.1)	0.06
DVT/*PE**	32 (7.1)	19 (10.9)	0.17
Isolated PE/*Izolovana PE*	35 (7.8)	20 (11.4)	0.198
Superficial/*Površinska*	34 (7.6)	23 (13.2)	0.04
Upper limb/*Ruke*	39 (8.7)	18 (10.9)	0.636
Splanchic/*Splanhička*	11 (2.4)	3 (1.8)	0.766
Sinus venous thrombosis/*Tromboza venskih sinusa*	17 (3.8)	1 (0.6)	0.03
Risk factor/*faktor rizika*			
Without/*Bez*	113 (25.2)	67 (38.5)	0.001
Pregnancy/*Trudnoća*	223 (49.8)	0	NA
Hormonal therapy/*Hormonska terapija*	28 (6.2)	1 (0.5)	NA
Infections/*Infekcija*	15 (3.3)	5 (2.8)	0.958
Surgical/*Operacija*	26 (5.8)	18 (10.3)	0.07
Malignancy/*Malignitet*	3 (0.7)	40 (23)	<0.000001
Trauma/*Povreda*	10 (2.2)	9 (5.1)	0.099
Obesity/*Gojaznost*	3 (0.7)	4 (2.3)	0.1
Varicose vein/*Varikoziteti*	6 (1.3)	9 (5.1)	0.01
Combine/*Kombinovano*	6 (1.3)	3 (1.7)	0.718
Comorbid disease/*Druge bolesti*	10 (2.2)	18 (10.3)	<0.0001
Physical effort/*Fizički napor*	4 (0.9)	0	0.580
	N	447	174

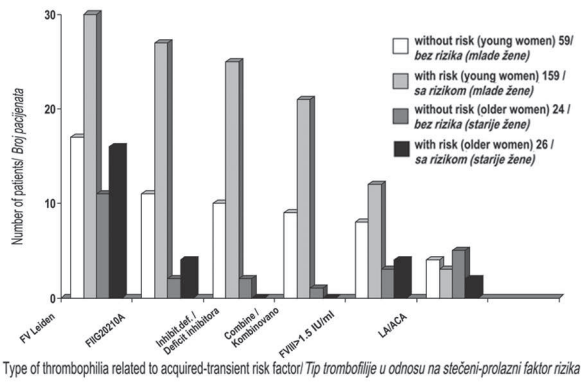
DVT - duboka venska tromboza, PE - plućna embolija

Table 2. Thrombophilia alterations
Tabela 2. *Prisustvo trombofilije*

	Young women/*Mlade žene* age/*starost* 18-45	Older women/*Starije žene* age/*starost* 45-75	p
Deficiency of natural inhibitors/*Nedostatak prirodnih inhibitora* n (%)			
(AT, PC, PS)	35 (7.8)	2 (1.1)	0.0009
FV Leiden mutation/*Mutacija*	88 (19.6)	27 (15.5)	0.277
Homozygous/*Homozigot*	1	2	
Heterozygous/*Heterozigot*	87	25	
FII G20210A mutation/*Mutacija*	38 (8.5)	6 (3.4)	0.04
Homozygous/*Homozigot*	4	1	
Heterozygous/*Heterozigot*	34	5	
Combined/*Kombinovani*	30 (6.7)	1 (0.6)	0.0006
FVIII > 1.5 iu/ml	20 (4.2)	7 (4.0)	0.977
Antiphospholipid syndrome *Antifosfolipidni sindrom*	7 (1.5)	7 (4.2)	0.144
n (%)	218 (48.7)	50 (28.7)	< 0.0001

AT - antitrombin, PC - protein C, PS - protein S, F - faktor

frequently than older women, who had distal or SVT more often. Regarding data from the Computerized Registry of Patients with Venous Thromboembolism (RIETE) study [8], distal DVT was less prevalent in women during pregnancy or puerperium, which was the most important risk factor among young women in our investigation. On the other hand, the most recent large observational study of patients with SVT has shown that this condition is typically diagnosed in outpatients, generally in women aged 60 years on average with high body weight, and/or a history of varicose veins [9]. This was confirmed among older women in our study. Data from both the RIETE [8] and our earlier study [10] showed that inherited thrombophilic alterations had no effect on the prevalence of distal DVT, which was confirmed in this study since the incidence of the inherited thrombophilia was almost double in the group of young women. That could have had an impact on the differences regarding the localization of thrombosis, especially in cases of thrombosis at unusual places (e.g. CVT). CVT was recently found to be strongly associated with congenital thrombophilia [11, 12]. The incidence of CVT is the highest in the third decade, and about 75% of all events occur in women with a strong association between CVT and two gender specific risk factors, such as the use of OC and pregnancy/postpartum [13], as confirmed in this study. In our group of young women, the development of CVT was associated with pregnancy/puerperium in 35%, or OC use in



Graph 1. Association of thrombophilia and acquired-transient risk factors
Grafikon 1. *Udruženost trombofilije i stečenog-prolaznog faktora rizika*

Table 3. Risk of recurrence
Tabela 3. *Rekurentne venske tromboze*

	Young women/*Mlade žene* age/*starost* 18-45	Older women/*Starije žene* age/*starost* 45-75	p
Number of women with RVTE/*Broj žena sa RVTE*	118 (26.3)	31 (17.8)	0.03
Time for the first recurrence */*Vreme za prvu rekurentnu trombozu*			
Mean (range)/*Prosek (raspon)*	5 (1-29)	4.8 (1-17)	0.588
N	447	174	

RVTE - recurrent venous thromboembolism/*rekurentni venski tromboembolizam*
*expressed in year/*izražen u godinama*

23% of cases and additionally potentiated with congenital thrombophilia in 41% of them. Contrary to that, only one CVT was observed among our older patients, in this case associated with a prothrombin G20210A mutation.

Among young women, the most important risk factor for first thrombosis was pregnancy and puerperium, while hormonal therapy was the second most important risk factor. The risk of occurrence of VTE in pregnant women is 5-fold higher than in non-pregnant women, and VTE is the most probable cause of death following delivery [14, 15]. On the other hand, hormonal therapy, especially in the presence of thrombophilia, is a strong risk for VTE [16]. These two transient risk factors inherent in women of reproductive age were found in 56% of our young patients. Spontaneous thrombosis without any particular risk occurred frequently among our older patients. More frequent occurrence of spontaneous thrombosis without any additional risk factors in this group could be explained by their age since the risk of thrombosis increases with age [17]. Regarding acquired risk factors associated with thrombosis in older women, a comorbid disease was the most important one, usually a malignant disease.

The frequency of congenital thrombophilia differed significantly between the two groups. Thus, incidences of an inhibitor deficiency, prothrombin G20210A mutation or combined thrombophilia were almost negligible in the older women. This difference results from the fact that a deficiency of natural inhibitors or combined thrombophilia, which are defined as severe thrombophilic conditions, are manifested very early and most carriers develop first thrombosis at an early age [18]. The patients with prothrombin G20210A were younger at their first VTE and had a higher rate of DVT accompanying PE than those with FV Leiden or no thrombophilia [10, 19]. One important observation from our current study relates to the finding that only the FV Leiden mutation, as an inherited thrombophilic alteration, was equally present in both groups of women. This mutation is a moderate thrombophilia alteration that often becomes clinically manifest in the presence of associated risk factors (e.g. pregnancy, surgery, trauma) and as such can appear for the first time in any period of life, as confirmed here. The second important observation concerning inherited thrombophilia is the finding that among young female carriers of thrombophilia, thrombosis occurred in three quarters of them during high-risk situations, such as pregnancy/puerperium or OC use. In their cases, FV Leiden and prothrombin mutations were the most frequent inherited thrombophilias combined with these risk factors, as shown previously [20–23], additionally emphasizing the multifactorial etiology of VTE. On the contrary, the effect of additional risk factors was much less pronounced among older female carriers of inherited thrombophilia.

Since 26.3% of the young women in our study group developed recurrent thrombosis in comparison with 17.8% of the older women, we assume that the higher prevalence of risk factors during the first event among young women may have an impact, especially given the higher incidence of inherited thrombophilia. It is also very important to note the influence of localization of thrombosis, bearing in mind the higher incidence of proximal DVT among young women. Similar findings regarding the localization and recurrence of thrombosis were observed earlier, where isolated distal DVT was associated with a lower risk of recurrence than proximal DVT or PE [24, 25]. On the other hand, inherited thrombophilic alterations, especially severe ones, such as deficiency of natural anticoagulants or combined thrombophilia are strong recurrence risk factors [26–30].

Among the limitations of our study that should be discussed is the fact that our study is retrospective, involving selected patients from two thrombosis centers, therefore the findings from our study should be confirmed in a further prospective studies.

Conclusion

Younger women developed more severe forms of thrombosis than the older ones. Inherited risk factor for thrombosis was detected in almost half of all young women, as opposed to less than 30% in elderly women. With the exception of factor V Leiden mutation, other types of congenital thrombophilia are almost negligible in the group of older women. Therefore, thrombophilia testing in case of first thrombosis is fully justified only in young women.

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